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Diastereoselective Intermolecular Cobalt-Catalyzed Reductive Aldol Reactions of α,β-Unsaturated Amides with Ketones

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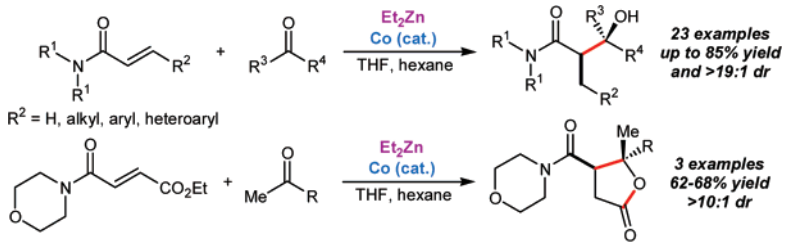
ABSTRACT



Under cobalt catalysis, diethylzinc mediates the conjugate reduction of α,β-unsaturated amides to produce ethylzinc enolates that react with ketones in situ to produce tertiary alcohol-containing aldol products with up to >19:1 diastereoselectivity.

Zinc enolates are an important class of reagents for organic synthesis, readily reacting with a range of electrophiles,[1−3] and exhibiting lower basicity and greater functional group compatibility compared to their alkali metal counterparts. There are several common methods to access zinc enolates using stoichiometric zinc sources.[4,5]

The first method involves the transmetalation of an alkali metal enolate with a zinc halide, which necessitates the use of strong alkali metal amide bases at low temperatures in a prior enolization step that may be accompanied by regioselectivity problems when more than one site of enolization is available.

The second method involves the reaction of a suitable zinc source (zinc powder, organozinc reagents) with an α-halocarbonyl compound, with or without catalysis.[1] Advantages of this method are the use of milder, less basic conditions, often complete regioselectivity, and the ability to have the electrophile present in situ. The utility of this methodology is evidenced by the Reformatsky reaction and its variants,

(1) For the reaction of zinc enolates with aldehydes and ketones, see: (a) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210−1211. For reviews of the Reformatsky reaction, see: (b) Fürstner, A. *Synthesis* **1989**, 571−590. (c) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325−9374. (d) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2568−2571.

(2) For selected examples of the reaction of zinc enolates with imines, see: (a) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255−2256. (b) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143−2150. (c) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600−3603.

(3) For the use of zinc enolates in palladium-catalyzed α-arylations, see: (a) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976−4985. (b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176−11177. (c) Bentz, E.; Moloney, M. G.; Westaway, S. M. *Tetrahedron Lett.* **2004**, *40*, 7395−7397.

(4) For other recent methods of stoichiometric zinc enolate formation not discussed above, see: (a) Ikeda, Z.; Hirayama, T.; Matsubara, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8200−8203. (b) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *16*, 4105−4108. (c) Hlavinka, M. L.; Hagadorn, J. R. *Tetrahedron Lett.* **2006**, *47*, 5049−5053. (d) Hlavinka, M. L.; Greco, J. F.; Hagadorn, J. R. *Chem. Commun.* **2005**, 5304−5306.

(5) For selected examples of catalytic zinc enolate generation using substoichiometric quantities of chiral bimetallic zinc complexes, see: (a) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777−8785. (b) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582−2590. (c) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169−2178. (d) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003−6005. (e) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778−2779. (f) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602−8603. (g) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368. (h) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004.

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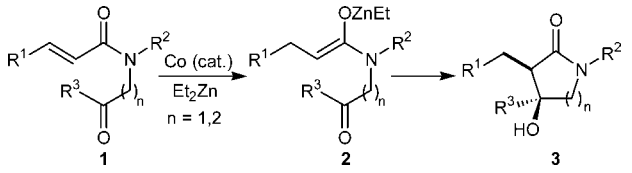
which are still widely practiced in synthesis today.[1] However, the use of α-halocarbonyls compounds as zinc enolate precursors is not without limitations. Although simple α-halocarbonyls are readily available, more complex substrates require the installation of the halide in a separate step, which may pose problems when sensitive functional groups are present.

A third method to prepare zinc enolates is via the catalytic conjugate addition of organozinc reagents to an α,β-unsaturated carbonyl compound.[6] Although this method may benefit from the advantages of chemically robust, readily available precursors and high regioselectivity of enolate formation under mild conditions, the α,β-unsaturated carbonyl compounds that may be employed are often restricted to enones. More synthetically versatile but less reactive α,β-unsaturated carboxylic acid derivatives remain challenging substrates for catalytic organozinc conjugate additions.[7] Furthermore, this method necessitates the formation of a carbon−carbon bond and often a new stereogenic center. Although desired in some cases, other synthetic applications may not require this increase in complexity. Therefore, the development of an analogous method that results in the formation of a *carbon−hydrogen* bond using α,β-unsaturated carboxylic acid derivatives should be of utility.

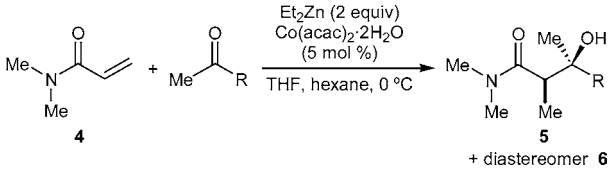
We recently reported a method for the generation of zinc enolates that meets these criteria.[8] In the presence of a substoichiometric quantity of a cobalt salt, diethylzinc mediates the conjugate reduction of α,β-unsaturated amides **1** to form ethylzinc enolates **2** that participate in high-yielding diastereoselective aldol cyclizations with tethered ketone electrophiles (Scheme 1). Herein, we report that the Co/Et_2Zn system is able to promote the corresponding intermolecular reductive aldol reactions[9] of α,β-unsaturated amides with ketones[10] in situ to furnish tertiary alcohol-containing aldol products.

Scheme 1. Cobalt-Catalyzed Reductive Aldol Cyclization



Our studies commenced with the reactions of a range of ketones with commercially available *N*,*N*-dimethylacrylamide (**4**) (Table 1) and 4-acryloylmorpholine (**7**) (Table 2). Under conditions similar to those employed in our previous study,[8] amides **4** and **7** underwent smooth reductive aldol reactions with a range of acetophenone derivatives containing substituents of varying electronic properties to provide the corresponding aldol products with up to 9:1 diastereomeric ratio and 85% isolated yield of the major diastereomer (Table 1, entries 1−6, and Table 2, entries 1−3). The beneficial effect of ortho-substitution in the acetophenone on the diastereoselectivity of the reaction should be noted (Table 1, entries 2 and 5, and Table 2, entry 2). Reactions with ketones containing naphthyl and furyl substituents were successful (Table 1, entries 7−8, and Table 2, entries 4−5),

Table 1. Cobalt-Catalyzed Reductive Aldol Reactions of *N*,*N*-Dimethylacrylamide (**4**) with Representative Ketones[a]



entry	R	product(s)	dr[b]	yield(s) (%)[c]
1	Ph	**5a**	5:1	75
2	2-MePh	**5b**	9:1	68
3	4-MePh	**5c**	5.5:1	79
4	4-MeOPh	**5d**	6:1	84
5	2-BrPh	**5e**	7:1	56
6	4-BrPh	**5f**, **6f**	3.5:1	73 (15)
7	2-naphthyl	**5g**	5:1	78
8	2-furyl	**5h**, **6h**	2.5:1	66 (25)

[a] Reactions were conducted using 1.0 mmol of **4** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1−29 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

(6) For an early report, see: (a) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141−5144. For selected examples of sequential catalytic asymmetric conjugate addition−electrophilic trapping reactions using organozinc reagents, see: (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620−2623. (c) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244−7254. (d) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104−1105. (e) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358−4359. (f) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (g) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (h) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528−4529.

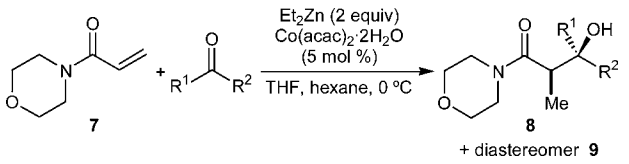
(7) For recent examples of catalytic enantioselective conjugate additions of organozinc reagents to α,β-unsaturated carboxylic acid derivatives, see: (a) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306−5310. (b) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279. (c) Schuppan, J.; Minaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 792−793.

(8) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729−3732.

(9) For cobalt-catalyzed reductive aldol reactions, see: (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005−2008. (b) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448−9453. For reductive aldol reactions catalyzed by other metals, see references cited within: (c) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2006**, *72*, 1063−1072. For relevant reviews, see: (d) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105−137. (e) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953−3958. (f) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653−661. (g) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12−21. (h) Chiu, P. *Synthesis* **2004**, 2210−2215. (i) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135−142.

(10) For catalytic enantioselective reductive aldol reactions with ketones, see: (a) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225−4228. (b) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292−1297. (c) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403−1407. (d) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440−14441. (e) Shiomi, T.; Nishiyama, H. *Org. Lett.* **2007**, *9*, 1651−1654.

Table 2. Cobalt-Catalyzed Reductive Aldol Reactions of 4-Acryloylmorpholine (**7**) with Representative Ketones[a]



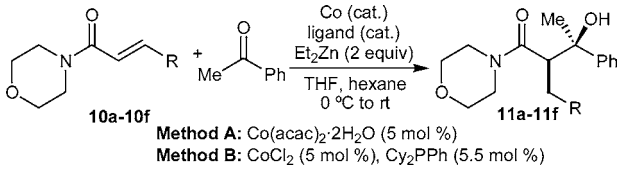
entry	R^1	R^2	product(s)	dr[b]	yield(s) (%)[c]
1	Me	Ph	**8a**	5.5:1	80
2	Me	2-MePh	**8b**	9:1	84
3	Me	4-MeOPh	**8c**	6.5:1	85
4	Me	2-naphthyl	**8d**, **9d**	4.5:1	82 (17)
5	Me	2-furyl	**8e**, **9e**	3:1	72 (22)
6	Me	*i*-Pr	**8f**, **9f**	1:1	33 (31)
7	Me	*i*-Bu	**8g**, **9g**	1:1	35 (36)
8	Et	Ph	**8h**	6:1	75
9	Ph	Ph	**8i**	na	62

[a] Reactions were conducted using 1.0 mmol of **7** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 3−7 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

as was reaction of **7** with propiophenone (Table 2, entry 8) and benzophenone (Table 2, entry 9). Although aliphatic ketones were also found to be competent substrates from a reactivity standpoint, their reactions exhibit no diastereoselection (Table 2, entries 6−7).

Table 3 presents the results of reactions of a range of β-substituted α,β-unsaturated morpholine amides with acetophenone. These data illustrate that substitution at the β-position of the unsaturated amide has a beneficial impact on reaction diastereoselectivity (≥9:1). Both linear and branched alkyl groups were tolerated (entries 1−3), as were aromatic (entries 4−5) and heteroaromatic (entry 6) substituents. With alkyl-substituted morpholine amides **10a**−**10c**, incomplete conversions were observed using $Co(acac)_2{\cdot}2H_2O$ as the precatalyst, but the combination of $CoCl_2$ and Cy_2PPh provided improved results (entries 1−3).[8]

Table 3. Cobalt-Catalyzed Reductive Aldol Reactions of Acetophenone with Representative α,β-Unsaturated Morpholine Amides[a]

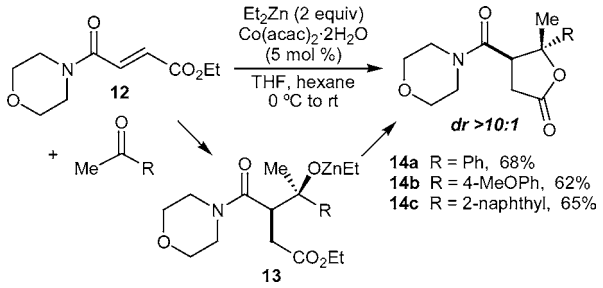


entry	method	R	substrate	product	dr[b]	yield (%)[c]
1	B	Me	**10a**	**11a**	>19:1	76
2	B	*i*-Bu	**10b**	**11b**	>19:1	85
3	B	CH_2CH_2Ph	**10c**	**11c**	16:1	81[d]
4	A	Ph	**10d**	**11d**	>19:1	71
5	A	2-naphthyl	**10e**	**11e**	10:1	74
6	A	2-furyl	**10f**	**11f**	9:1	84

[a] Reactions were conducted using 1.0 mmol of **10a**−**10f** and 1.1 mmol of acetophenone in THF (10 mL) and hexane (2 mL) for 2−6 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer. [d] Yield of a 16:1 inseparable mixture of diastereomers.

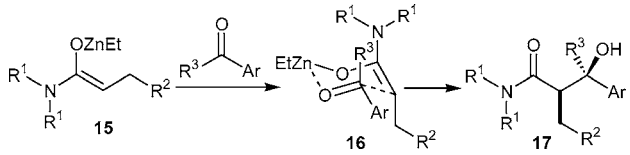
Unsaturated amide **12** provided an interesting regiochemical problem, because it contains an α,β-unsaturated amide that also forms part of an α,β-unsaturated ester. It was therefore of interest to observe whether conjugate reduction would be successful, and if so, whether an amide enolate or an ester enolate would result. In the event, reductive aldol reaction of **12** with a range of methyl ketones provided lactones **14a**−**14c** in 62−68% yield as a result of the intermediate zinc alkoxides **13** cyclizing onto the pendant ethyl ester (Scheme 2). These experiments demonstrate that conjugate reduction of **12** occurred to generate the morpholine amide enolate preferentially.[11]

Scheme 2. Reductive Aldol Coupling of **12** with Various Ketones Producing Lactones **14a**−**14c**



The diastereochemical outcomes of these reactions[12] are consistent with the participation of *Z*-zinc enolates **15** and chelated chairlike Zimmerman−Traxler transition states[13] in which the larger aromatic substituent of the ketone prefers to reside in a less sterically hindered pseudoequatorial position (as in **16**; Scheme 3).

Scheme 3. Model for Stereochemical Outcome



In conclusion, zinc enolates generated through cobalt-catalyzed conjugate reduction of α,β-unsaturated amides

(11) α,β-Unsaturated esters do undergo reductive aldol reactions with ketones using Co/Et_2Zn, but with low diastereoselectivities. For example, methyl cinnamate reacts with acetophenone to produce a ca. 1:1 mixture of diastereomers.

(12) The relative stereochemistry of the known compound **5a** was assigned by comparison with literature spectral data. The relative stereochemistries of **5c**, **8f**, and **8g** were determined by X-ray crystallography. The stereochemistries of the remaining aldol products were assigned by analogy. See the Supporting Information for details.

using diethylzinc as the stoichiometric reductant undergo in situ diastereoselective aldol reactions with ketones to provide tertiary β-hydroxycarbonyl compounds. Further applications of this methodology will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds (PDF); crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.